3. REMARKS

Claims 1 to 11 were pending in the instant application. By this amendment, Claims 8, 10 and 11 have been canceled without prejudice to applicants' right to pursue the subject matter of the canceled claims in other applications, and Claims 1, 4, 5, and 7 have been amended to comply with the Examiner's restriction requirement and requirement for species election.

In addition, Claim 1, and claims dependent thereon, have been amended to specify the peripheral administration of a *non-toxic* amount of erythropoietin. The instant application fully describes and enables the use of such *non-toxic,* excitable tissue enhancing amount of recombinant EPO (*e.g.*, see Summary of the Invention at p.4, *ll.* 26-27). The specification further describes formulations and non-toxic dosages of erythropoietin that could be used to treat and protect myocardial infarction (specification at p.22, *l.* 25 to p.24, *l.* 6; see also p.4, *ll.* 26-27). In addition, the specification enumerates the factors that should be considered to determine appropriate *non-toxic* dosage of erythropoietin, and specifies that the skilled practitioner should readily be able to make such a determination according to standard clinical techniques (see p.22, *l.* 32 to p.23, *l.* 9).[1] Therefore, no new matter is added by this amendment, which is fully supported by the specification and claims as originally filed.

Therefore, Claims 1-7, and 9 will be pending upon entry of the instant amendment. Entry of the amendments and the remarks made herein into the record for the above-identified application is respectfully requested.

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[1] In this regard, the Examiner's attention is invited to the 2000 edition of the Physicians' Desk Reference ("PDR"), the art-accepted standard reference manual for practitioners at the relevant time; and, in particular, the section of the PDR relating to erythropoietin (see PDR, pp.519-525 and 2125-2131, a copy of which is provided herewith as Exhibit C). The PDR shows that, depending on the patient population being treated with erythropoietin, different hematocrit ranges are targeted to avoid toxicity. The PDR shows that practitioners monitor the patient's hematocrit during therapy with erythropoietin and, to avoid toxicity, adjust the dose and/or withhold treatment if the patient's hematocrit approaches or exceeds the upper limits of a target range. Therefore, the skilled practitioner, armed with the teachings of the instant specification, would be able to administer excitable tissue enhancing doses of erythropoietin, yet avoid toxic side effects, *e.g.*, simply by monitoring the patient's hematocrit and adjusting the dosing of erythropoietin to maintain the patient's hematocrit within the desired target range. Given this direction, the skilled practitioner would be able to make appropriate determinations and choices using ordinary skill.

3.1 PRIORITY

The Examiner has indicated that the application does not comply with the requirements for a priority claim for a utility application filed on or after November 29, 2000.

In response, Applicants respectfully submit that the priority claim of the instant application complies with the requirements for a priority claim under 37 C.F.R. § 1.78. The instant application claims priority under 35 U.S.C. §120 to Application no. 09/547,220, filed April 11, 2000 ("the '220 application"), and under 35 U.S.C. §119(e) to U.S. provisional patent Application No. 60/129,131 filed April 13, 1999 ("the '131 application") (see the copy of the Information Data Sheet, and the return receipt postcard date-stamped February 22, 2003, which is enclosed herewith as Exhibit A). Specific reference to the '131 application was made on the first line of page 1 of the specification of the instant application as originally filed, and the specification was amended to include a specific reference to the parent '220 application in paragraph 3 of the Request for Filing A Divisional Application (hereinafter "the Request") (a copy of page 1 of the specification, the Request, and the return receipt postcard date-stamped November 21, 2000 are transmitted herewith as Exhibit B).

As such, applicant believes the priority claim of the instant application complies with the requirements under 37 C.F.R. § 1.78 for applications filed before November 29, 2000.

3.2 THE DOUBLE-PATENTING REJECTIONS SHOULD BE WITHDRAWN

Claim 1 is provisionally rejected for obvious-type double patenting over claim 1 of copending Applications Nos. 09/547,220 ("the '220 application"), 09/717,053 ("the '053 application"), and 09/716,960 ("the '960 application"). Applicants submit that this rejection is in error, for the following reasons.

Obviousness-type double patenting requires rejection of a patent claim when the claimed subject matter of a patent is not patentably distinct from the subject matter claimed in a commonly owned patent when the issuance of a second patent would provide unjustified extension of the term of the right to exclude granted by a patent. See *Eli Lilly and Co. v. Barr Labs., Inc.*, 222 F.3d 973 (Fed. Cir. 2000). According to the Manual of Patent Examining Procedure ("MPEP"), when analyzing whether a nonstatutory basis for a double-patenting rejection exists, "the first question to be asked is — does any *claim* in the application define an invention that is merely an obvious variation of an invention *claimed* in the patent?" (Emphasis added.) MPEP, Section 804 at p.22 (Eighth Edition, August, 2001).

When considering whether the invention defined in a *claim* of an application is an obvious variation of the invention defined in the *claim* of a patent, the disclosure of the patent may not be used as prior art. MPEP at p.800-22, ¶ 7.

Applying the legal standard above, the method of Claim 1 of the instant application is patentably distinct, and non-obvious over, Claim 1 the '220 application. Claim 1 of the instant application is drawn to a method for enhancing the function of normal or abnormal excitable tissue in a mammal comprising administering peripherally to said mammal a peripherally effective excitable tissue enhancing amount of an EPO, an EPO receptor activity modulator, an EPO-activated receptor modulator, or combination thereof. The method of Claim 1 is based on the discovery by the applicants that erythropoietin can cross endothelial cell barriers, and can thus be used to enhance learning and memory in normal and abnormal mammals. In contrast, Claim 1 of the '220 application is drawn to a method for treating cerebral ischemia in a mammal comprising peripherally administering to said mammal a non-toxic amount of erythropoietin effective to exert a neuroprotective effect, based on the ability of erythropoietin to cross the blood-brain barrier. Without the additional information provided by the disclosure of the instant application that erythropoietin can be used to enhance learning and memory, one of skill in the art would not understand from reading Claim 1 of the '220 application that that erythropoietin could be used to *enhance* the function of excitable tissue. It is well-established, however, that the disclosure (of the '220 application) may not be used to make obvious the rejected claim, *i.e.*, Claim 1 of the instant application, in an obviousness-type double-patenting rejection (see MPEP at p.800-22, ¶ 7). Thus, while one of skill in the art would understand from the invention defined in Claim 1 of the '220 application that erythropoietin crosses the blood-brain barrier, without reading the disclosure of the instant application the skilled artisan would not possibly conclude that erythropoietin can be used to enhance excitable tissue function and improve memory and learning in mammals. Thus, the invention defined in Claim 1 of the instant application cannot be considered an obvious variation of the invention defined Claim 1 of the '220 application, and, as such, is patentably distinct and non-obvious over Claim 1 of the '220 application.

Likewise, the method of Claim 1 of the instant application is patentably distinct and non-obvious over Claim 1 the '053 application. Claim 1 of the '053 application is drawn to a method for prevention or treatment of a neuromuscular or muscular condition comprising administering peripherally to a mammal in need of treatment for a neuromuscular or muscular condition a non-toxic amount of EPO effective for the protection of a heart tissue.

Only by deviating from claims and reading the additional disclosure provided by the specification, which is not the standard for obvious-type double patenting, would the skilled artisan know that erythropoietin can cross other endothelial barriers and used to enhance the function of excitable tissue. Thus, the invention defined in Claim 1 of the instant application cannot be considered an obvious variation of the invention defined Claim 1 of the '053 application, and, as such, is patentably distinct and non-obvious over Claim 1 of the '053 application.

By the same reasoning, the method of Claim 1 of the instant application is also patentably distinct, and non-obvious over, Claim 1 the '960 application. Claim 1 the '960 application is drawn to a method for preventing or treating a neurodegenerative condition comprising peripherally administering to said mammal an effective amount of erythropoietin. The skilled artisan would not be able to understand, based on the claimed invention alone, ability of erythropoietin to prevent or treat neurodegenerative conditions provided by the invention defined by Claim 1 of the '960 application, that erythropoietin can cross other endothelial barriers and enhance the function of excitable tissue. Thus, the invention defined in Claim 1 of the instant application cannot be considered an obvious variation of the invention defined Claim 1 of the '960 application, and, as such, is patentably distinct and non-obvious over Claim 1 of the '960 application.

Accordingly, applicant respectfully submits that the rejection for obviousness-type double-patenting is in error and requests its withdrawal.

3.3 THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 1-7, 9 and 10 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner argues that the specification is enabling for a method for peripheral administration of EPO in a mammal for enhancing the function of *normal* excitable tissue, but is not enabling for enhancing the function of *abnormal* excitable tissue.

The applicants' teachings coupled with the experimental data disclosed in the specification are sufficient to enable one of skill in the art to practice the instant invention in a human subject. As noted by the Examiner, the instant specification does, indeed, provide explicit teaching regarding peripheral administration of EPO in a mammal for enhancing the function of normal excitable tissue (see Section 5.2.1, p.12, *l.*7 to p.13, *l.*14) which describes methods which can be used to test art-accepted learning or cognitive function, such as the Morris water maze test and the conditioned taste aversion test (CTA), exemplified in the

Examples presented in Sections 6 and 7, respectively. The efficacy of the claimed methods is actually demonstrated in working examples using art-accepted animal models of the human conditions. The efficacy of the claimed methods have since been corroborated, as demonstrated by the data attached hereto as Exhibit C.

Exhibit D is a compilation of data presented as examples in applicants' copending applications which utilize the teaching provided in the instant specification to corroborate the method for enhancing learning and memory in mammals with *abnormal* excitable tissue by peripherally administering EPO.

In particular, Figure 18 of Exhibit D corroborates the methods for the enhancement of abnormal tissue in a mammal using EPO, as described on p.12, *l.*7 to p.13, *l.*14 of the application as originally filed. As shown in Figure 18, using the Morris water maze test, administration of EPO restored diminished cognitive function to mice that had received brain trauma (see Exhibit D, p.88, ¶ 1, and Figure 18). As shown in Figure 19, EPO improved the brain function of traumatized mice, as manifested by improved swim times, even when EPO was administered 30 days after the brain trauma (see Exhibit D, p.88, ¶ 1: Figure 19).

Figure 20 of Exhibit D further corroborates methods for the use of EPO to enhance the function of abnormal cerebral tissue in a kainate model of cerebral toxicity (see Exhibit D, p.88; Figure 20). Figure 20 shows the results of a focal ischemia model in which dose response was performed with two forms of EPO, unmodified EPO and asialo-EPO ("WP-170"). As shown in Figure 20, both forms of EPO are efficacious at enhancing function in the kainate-treated animals, as shown by increased time to death.

In summary, then, the results presented in Exhibit D definitively corroborate the teaching of the instant application, using widely accepted and art-recognized animal models, so that the skilled artisan is able to carry out the claimed methods for enhancing learning and memory in mammals with *abnormal* excitable tissue by peripherally administering EPO, without undue experimentation.

For each of the reasons set forth above, applicants assert that the specification fully describes and enables the claimed methods of the invention and, as such, respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

3.4 THE REJECTIONS UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN

Claims 1-7, 9 and 10 are rejected under 35 U.S.C. 102(b) are rejected as anticipated by Grimm *et al.* (IDS#4 BC; 1990, Kidney International 38: 480-486; "Grimm"), and also by

Marsh *et al.* (IDS#4 BP; 1990, Kidney International 39: 155-163; "Marsh"). The Examiner alleges that both Grimm and Marsh teach that peripherally administering recombinant human erythropoietin in hemodialysis and/or anemic patients can improve brain and/or cognitive function.

In response, Claims 1-7 and 9 have been amended to specify dosage regimens of EPO sufficient to cross an endothelial cell barrier effective for enhancement of excitable tissue, yet which are not toxic - - *e.g.*, do *not* significantly cause an increase in hematocrit (see specification at p.13, *ll.*19-21 and Section 5.4.1, especially p.22, *ll.*35-31 and p.23, *l.*28 to p.24, *l.*12). Applicants submit that the amended claims are not anticipated by Grimm or Marsh, as set forth below.

The present invention is based, in part, on the applicants' unexpected discovery that peripherally administered EPO is transcytosed across the blood brain barrier, becoming associated with cells of the central nervous system ("CNS"), such as neurons and astrocytes.[2] Applicants have demonstrated (and others have since confirmed) that when high doses of EPO are peripherally administered to a mammal *in vivo*, the transcytosed EPO can be detected in the cerebral spinal fluid ("CSF").[3] The transcytosed EPO can exert an enhancing effect on such excitable cells and tissues, *i.e.*, cells and tissues which possess receptors for EPO. In the presently claimed invention, EPO is peripherally administered at doses sufficient for transcytosis and enhancement of excitable cells and tissues (such as administering it as a bolus), yet for durations that are too short to result in a clinically significant increase in hematocrit. These dosage regimens result in fewer side effects associated with unwanted increase in hematocrit and blood viscosity.

In contrast, there is no recognition in either Grimm or Marsh of the unexpected ability of EPO to cross an endothelial cell barrier, which forms the basis for the methods using high-dose regimens of the claimed invention. Both Grimm and Marsh teach treating chronic hemodialysis patients, *i.e.*, chronic kidney dialysis patients suffering from severe anemia caused by a deficiency of erythropoietin whose anemia results in impaired cognitive function, exercise capacity and quality of life. Both Grimm and Marsh focus on the treatment of anemia by administering EPO to raise the hematocrit, thereby correcting the anemia, which,

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[2] See application as originally filed at Example 1 at pp.28-29 and Figure 1; Brines *et al.*, 2000, Proc. Natl. Acad. Sci. USA 97:10526-31, p.10531

[3] *Id.*; Juul *et al.*, 2001, Society for Neuroscience Abstracts 27(1):929; and Farrell *et al.*, 2001, Blood 98(11):148b.

according to Grimm, is the underlying cause of the brain dysfunction. As explained by Grimm, the results of the study confirm the beneficial mental effects of recombinant human EPO in these patients, and strongly suggest that the beneficial effect "is due to the partial correction of anemia and not related to other effects" (Grimm, last sentence on p.484 to top of 485; p.484, col 1, *l.* 22). Marsh's study concurs with Grimm's conclusions. For example, in the Discussion, Marsh concludes that their study, as well as a number of similar studies that assess the effects of rhuEPO treatment in renal patients stabilized on hemodialysis, "indicate that the correction of anemia improves aspects of brain/cognitive function" (Marsh, p.161, col.2, last ¶). In other words, Grimm and Marsh both teach the use of a sufficient amount and dosage regimen of EPO to cause an *increase* in hematocrit in these anemic patients (see p.481, Table 1A).[4]

In contrast, the methods of the instant invention require treating mammals having either normal or abnormal excitable tissue, *i.e.*, *regardless* of the effect on erythropoietic activity or on hematocrit. Moreover, the presently claimed methods use amounts and dosage regimens of EPO sufficient to cross an endothelial cell barrier effective, yet which are not toxic - - *e.g.*, do *not* significantly cause an increase in hematocrit (see specification at p.13, *ll.*19-21 and Section 5.4.1, especially p.22, *ll.*35-31, and p.23, *l.*28 to p.24, *l.*12). Thus, neither Grimm nor Marsh anticipate the claimed methods.

For all the reasons discussed above, neither Grimm nor Marsh disclose or suggest the claims of the instant invention. Accordingly, applicant respectfully requests that the rejection of Claims 1-7, 9, and 10 under 35 U.S.C. 102(b) be withdrawn.

3.5 MISCELLANEOUS MATTERS

Applicants take this opportunity to bring to the attention of the Examiner the reference Albayrak *et al.*, 1997, ACTA Neuropathol. 94: 158-163 ("Albayrak"), a copy of which is provided herewith as Exhibit E. Applicants believe Albayrak supports the patentability of the instantly claimed invention, and is merely cumulative to information already of record in the instant application, and therefore is not material to patentability under Rule 1.56(b). Although Albayrak has not been cited in connection with any of the applicants' counterpart foreign applications, we take this opportunity to note that Albayrak was cited by

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[4] Grimm used low doses of EPO administered chronically, *e.g.*, 70 ± 15U/kg to 94 ± 27U/kg of EPO thrice weekly (*i.e.*, 210 to 282 U/kg per week) over a duration of 4.7 ± 1.2 months (Grimm, p.480, col 2, last paragraph and Table 1B).

the European Patent Office in connection with the European examination of WO 00/35475 (Ref. AR of record). Applicants note that reference AR designates the United States, and according to the USPTO records, entered the national stage on June 28, 2001 as U.S. Application No. 09/868,089.

CONCLUSIONS

Applicants respectfully request that the foregoing amendments and remarks be made of record in the file history of the instant application. Applicants estimate that the remarks and amendments made herein now place the pending claims in condition for allowance.

Respectfully submitted,

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Enclosures